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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/028,514	02/23/1998	STEPHEN F. GORFIEN	0942.4110002	4800

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EXAMINER	
WARE, DEBORAH K	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/028,514	GORFIEN ET AL.	
	Examiner	Art Unit	
	Deborah K. Ware	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *79-82-106-109, 112, 143-153, 155 and 156* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-17,20-24,27-37,73-77,140 and 157-174* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,6-17,20-24,27-37,73-77,79-82,106-109,112,140,143-153 and 155-174.

DETAILED ACTION

Claims 1-3, 6-17, 20-24, 27-37, 73-77, 79-82, 106-109, 112, 140 and 143-153 and 155-174 remain of record and pending in the instantly filed case.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on September 20, 2004, has been received and entered. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A copy of the PTO-1449 Form is enclosed herewith in response to Applicants' request in their response.

Papers

The extension of time, amendment and arguments filed September 20, 2004, have been received and entered of record.

Election/Restriction

This application contains claims 79-82, 106-109, 112, 143-153, 155 and 156 drawn to an invention nonelected with traverse in Paper No. filed May 20, 2002. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 79-82, 106-109, 112, 143-153, 155 and 156 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s) and for reasons of record, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

Claim 1-3, 6-17, 20-24, 27-37, 73-77, 140, and 157-174 are presented for reconsideration on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1, 6-17, 20-22, 27-37, 73-77, 140, 158 and 162 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polyanionic compound which is a polysulfonated or polysulfated compound as in claim 2, does not reasonably provide enablement for a polycationic compound or other polyanionic compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice and carry out the invention commensurate in scope with these claims. The exemplifed disclosure only enables a polysulfonated or polysulfated polyanionic compound in a serum free medium. There is no disclosure in the specfication as to how one of skill in the art would practice the claimed invention using a polycationic compound or another polyanionic compound in a medium that is serum free. There would be a high degree of unpredictability in this art to carry out the claimed method *for any mammalian cell type* using a polycationic compound since there are no examples disclosed in the instant specification to demonstrate that the same can be performed with any predictable positive outcome for viable cell recovery. Therefore, there would be an undue burden of experimentation placed upon one of skill in this art to carry out the claimed invention.

The claims are not considered to be enabled for the scope as claimed and should be limited to the enabling instant disclosure which appears to be directed to polyanionic compounds and no disclosure is evident in the instant specification regarding cationic compounds, or any polyanionic compound in a medium that is serum free.

Response to Arguments

Applicant's arguments filed September 20, 2004, have been fully considered but they are not persuasive. The argument that no evidence has been provided to support the above reasoning as to why the claims are not deemed enabling, is noted and herewith is provided a citation of a U. S. Patent 5,627,159 document which teaches at column 1, lines 35-40, polycationic compounds such as POLYBRENE is toxic to mammalian cells in the absence of serum. Therefore, based on this evidence, this polycationic compound will not work for culturing mammalian cells. Thus, for one of skill to have to research and test for each and every polycationic compound for which to determine whether or not it can be used in Applicants' claimed methods is burdensome to one of ordinary skill in the art and such testing is expensive as well. This evidence presents the facts surrounding the use of any and all polycationic compounds under any set of culturing conditions and for any cell types as claimed. Furthermore, Applicants' own specification provides no guidance to one of ordinary skill in the art to select for any preferred polycationic compound. Upon a reading of Applicants' own specification one of skill in the art is led to believe that any polycationic compound can work. However, as the evidence shows this is not the case. Furthermore, such evidence would lead one to recognize a polyanionic compound would require a great amount of experimentation

on the part of the ordinary artisan to determine whether or not it can work to as set forth in the claimed methods. Therefore, Applicants' arguments are not deemed persuasive and the rejection is maintained in part with respect to not being enabled for any and all polycationic compound or the use of any and all polyanionic compounds.

Claim Rejections - 35 USC § 103

Claims 1-3, 6-14, 22-24, 27-32, 35-37, 140, and 157-160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mignot et al in view of Cheesebeuf et al, Parenteau et al and Cleveland et al.

Claims are drawn to a method of cultivating a mammalian cell comprising obtaining a mammalian cell and contacting the cell with a serum free and protein free or basal culture medium containing polysulfonated polyanionic compounds or polycationic compounds. The medium can have a IX or 10X medium formulation, can contain amino acids such as L-alanine, and various other ingredients, and supplements such as heparin and organic peptides, vitamins such as biotin, salts such as calcium. The cell types can be of epithelial (normal or abnormal such as a transformed cell) and of human origin. The serum free can be free of animal derived components. Further a method of replacing protein in a mammalian cell culture medium is claimed which comprises eliminating insulin and transferrin and replacing them with zinc and iron in the medium. The medium may not contain dextran sulfate.

Mignot et al is discussed above.

Cheesebeuf et al teach basal medium for culturing animal cells and can be devoid of animal derived components such as hormones and growth factors, note col. 2,

lines 35-40 and col. 3 lines 20-25, 45-46. **Further, at column 4, lines 55-65, suspension culturing of cells is taught to be employed by their culture processes.**

Parenteau et al teach a method of culturing a mammalian cell in a culture medium using IX formulation mediums that iron can be used in place of transferrin, note col. 5, line 28. **Further, at column 22, lines 9-18, they teach that suspension culturing of cells is employed.**

Cleveland et al teach a protein free culture medium for culturing mammalian cells wherein the elimination of albumin, transferrin and insulin is an important advance in mammalian cell culture media. Note col. 3, lines 35-40 and 55-69.

The claims differ from Mignot et al in that certain claimed features are not disclosed such as components of culture media, IX formula media, elimination of transferrin and insulin, etc.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Mignot et al, Cheesbeuf et al, Parenteau et al and Cleveland et al to obtain a mammalian cell and contacting said cell with a basal serum free, protein free, non-animal derived cell culture medium containing IX formulation ingredients and to replace transferrin with iron and insulin with zinc, therein. Further to concentrate the medium formulation to a 10X concentrated medium formulation is well with the purview of an ordinary artisan. Each of the ingredients and supplements are disclosed by the cited prior art. To select for organic peptides such as soy peptides is also an obvious modification of the cited prior art. As well, the salt ingredient is disclosed by the cited prior art. To omit dextran sulfate or to include is also

well within the teachings of the cited prior art as discussed above. Various mammalian cell types are further disclosed, some of which are abnormal or transformed cells. One of skill in the art would have been motivated by the prior art to cultivate mammalian cells by contacting them with these well known ingredients in culture medium as disclosed by the prior art. **Also to employ suspension culturing is clearly an art recognized technique as taught by Cheesebeuf et al and Parenteau et al.** No unexpected successful results have been obtained. Therefore, in the absence of persuasive evidence to the contrary the claims are deemed *prima facie* obvious over the cited prior art.

Response to Amendment

Applicant's arguments filed September 20, 2004, have been fully considered but they are not persuasive. The argument that a case of obviousness can not be established unless all of the claim elements are taught or suggested is noted. However, the art as set forth above clearly do teach suspension culturing. Hence any insufficiency of Mignot et al is supplied by the secondary teachings of the applied cited prior art. Note that Parenteau and Cheesebeuf et al both teach suspension cell culturing, see above. Also replacement media is well recognized in the art and to eliminate transferring and insulin and to select for components such as Zn^{2+} and Fe^{2+} or Fe^{3+} is clearly within the skill of an ordinary artisan. To eliminate and use the components is clearly taught and hence to replace one for the other is suggested. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or

modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the art does indeed teach the suspension culturing as well as the other process steps and one of skill would have been motivated by these combined teachings of the cited prior art. Therefore, the arguments are not deemed persuasive and the rejection is maintained.

Claims 33-34, 73-77 and 161-174 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mignot et al in view of Cheesebeuf et al, Parenteau et al and Cleveland et al. as applied to claims above, and further in view of Wang et al.

Claims are discussed above and are further drawn to culturing human cells selected from 293 embryonic kidney cells and method of producing a virus which includes the method steps as discussed above but also contacting cell with a virus to promote viral infection of the cell wherein the virus can be an adeno-assoicated virus and further method of cultivating 293 cells wherein the polysulfonated or polysulfated compound is dextran sulfate.

Each of Mignot et al in view of Cheesebeuf et al, Parenteau et al and Cleveland et al are discussed above.

Wang et al teach 293 cells and method of producing a virus which includes contacting cells with a virus to promote viral infection of the cell wherein the cell can be an adeno-associated virus. Note col. 16, lines 53-54 and col. 19, line 5.

The claims differ from Mignot as discussed above.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to cultivate cells as discussed above and further to cultivate 293 cells and produce a virus as disclosed by Wang et al under conditions disclosed by the cited prior art discussed above. Clearly one of skill would have been motivated to select for 293 cells which would have been a choice of functional equivalents available to the artisan. One of skill would have expected successful results and would have been motivated to produce a virus using the conditions of Mignot et al in view of Cheesebeuf et al, Parenteau et al and Cleveland et al., especially since Wang et al teach the same. Each of the claim features, **including cultivating a mammalian cell in suspension**, are disclosed or suggested by the cited prior art and are discussed above. Wang et al clearly teach any missing deficiencies of the cited prior art such as 293 cells and production of a virus via the step of contacting the cells with a virus. Further, the prior art does recognize that dextran sulfate can be used especially to prevent cell clumping. In the absence of unexpected successful results the claims are rendered *prima facie* obvious over the cited prior art.

Response to Arguments

Applicant's arguments filed September 20, 2004, have been fully considered but they are not persuasive. For reasons discussed above each of the claim features are taught, or at least suggested. Thus, this rejection is maintained for these reasons as well as those of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Claims 15-17 and 20-21 are considered to be free of the cited prior art and would be allowable if claim 15 is amended in line 11 by canceling "or polycationic" and inserting --selected from the group consisting of a polysulfonated compound and a polysulfated compound-- after "compound" .

All art-rejected claims fail to be patentably distinguishable over the state of the art discussed above. Therefore, these claims are properly rejected.

The remaining references listed on the enclosed PTO-892 and/or PTO-1449 are cited to further show the state of the art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah K. Ware whose telephone number is 571-272-0924. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah K. Ware
December 9, 2004

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1285